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ToC blurb
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Recent studies on melanosome formation have begun to provide insights into novel aspects of endosomal sorting involved in cell physiology, organelle biogenesis, and amyloid formation. Moreover, genetic disorders that affect the formation of melanosomes and other lysosome-related organelles are revealing the molecular machinery that controls specialized sorting events.

Online summary

- Melanosomes are specialised intracellular organelles of pigment cells in which melanin pigments are synthesized and stored. They are members of a family of cell type-specific lysosome-related organelles (LROs) that coexist with traditional endosomes and lysosomes and are generated from them through a progressive series of membrane sorting steps.

- Early stage melanosomes harbour intralumenal fibrils that have characteristics of pathogenic amyloid fibrils, and that serve in later stages to concentrate and detoxify melanin intermediates. Like many pathogenic amyloids, the fibrils consist at least predominantly of proteolytic fragments of a single protein, in this case the pigment cell-specific Pmel17.

- Pmel17 fibrils begin to form on intralumenal membranes of multivesicular early endosomes. Active sorting to these intralumenal membranes is required for fibril formation and is mediated by a ubiquitin- and ESCRT-independent mechanism requiring a lumenal determinant. Pmel17 is similarly sorted even when it is ectopically expressed in non-melanocytic cells, indicating that the mechanism is not limited to specialised cell types.

- Constituents of late stage, pigmented melanosomes are separately sorted from constituents of early stage melanosomes and late endosomes/ lysosomes within early endosomes. This process is disrupted in Hermansky-Pudlak syndrome (HPS), a group of genetic diseases that affect the formation of melanosomes and several other LROs by disabling one of several ubiquitous protein complexes involved in protein delivery to LROs.

- Biochemical analyses of the products of genes that are disrupted by HPS, coupled with analyses of melanosome cargo trafficking in melanocytes from human and murine HPS models, have revealed that the AP-3 clathrin adaptor complex and of Biogenesis of LRO complex (BLOC)-1 and -2 regulate at least two cargo trafficking pathways from early endosomes to melanosomes. AP-3 and BLOC-1 regulate cargo exit from distinct early

endosomal membrane domains, whereas BLOC-2 regulates cargo delivery to melanosomes downstream of BLOC-1.

- Genetic analyses indicate that specialised members of the Rab family of GTPases, including the tissue-specific Rab32 and Rab38, cooperate with AP-3 and BLOCs to regulate delivery of melanosome-bound cargo proteins. Cargo transport is also regulated by ubiquitous endosomal SNAREs, some of which interact with BLOCs and AP-3 and show increased expression in melanocytes relative to other cell types, and by SNARE-associated Sec1/Munc18 family members.

- Pigment cell-specific transmembrane ion transporters, a melanosome-associated G protein coupled receptor, and the γ-secretase-associated presenilins are required for proper melanosome biogenesis, and mutations within them alter trafficking between endosomes and melanosomes. These likely reflect generalized requirements for similar proteins in regulating formation of most conventional and specialised endosomal organelles.